Possible Risk of Endometriosis for Seveso, Italy, Residents: An Assessment of Exposure to Dioxin

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A recent study by Rier et al. showed that rhesus monkeys exposed daily for 4 years to 5 or 25 ppt of dioxin in food develop endometriosis, with incidence and severity related to dose. We aimed to determine whether the total time-integrated dioxin exposure of a human population could be comparable to that of Rier's monkeys. We selected a sample of residents of Seveso, Italy, who were acutely exposed to high levels of dioxin following an accident in 1976. We conducted a toxicokinetic analysis which takes into account species and exposure differences in dose and tming between humans and monkeys. The area under the time-concentration curve for dioxin in fat, which corresponds to cumulative exposure over time, ranges for some of the most heavily exposed Seveso residents from approximately 1.7×10^6 ppt-days to 1.1×10^8 ppt-days. These values exceed in all cases the values for the monkeys exposed to 25 ppt or 5 ppt. Given their exposure, the Seveso population should be an ideal epidemiologic cohort to rule out or confirm whether exposure to dioxin leads to an increased risk of endometriosis in humans. *Key words*: endometriosis, rhesus monkey, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, toxicokinetics. *Environ Health Perspect* 102:476–477(1994)

The recent work of Rier et al. (*1*) showed that adult female rhesus monkeys exposed daily for 4 years to 5 and 25 ppt of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in their food developed endometriosis during a 10-year follow-up period. The incidence and severity of endometriosis was dose related. These findings are extremely important because endometriosis is a significant cause of debilitating pain and infertility in women. We sought to determine whether the levels of total TCDD exposure of the monkeys are within the range of that observed in human populations. As an example, we examined the TCDD levels for a population acutely exposed, via ingestion, inhalation, or dermal contact, after a chemical plant explosion in Seveso, Italy, in 1976. A simple toxicokinetic analysis aimed at comparing monkey and human total exposure shows the potential for an increased risk of endometriosis for the Seveso population.

Our toxicokinetic analysis takes into account species and exposure differences in dose and timing between humans and monkeys through modeling and use of species-specific parameters. The results are independent of the route of absorption differences because they are based on measured internal (blood or fat) concentration data. The exposures for humans in Seveso and monkeys in the Rier et al. study are comparable because for both the exposure was predominantly to TCDD with no significant exposure to the other polychlorinated dibenzo-*p*-dioxin and polychlorinated dibenzofuran congeners (*2*) Total exposure is estimated though the area under time-concentration curve (AUC), which is a standard way to estimate long-term internal exposure to bioaccumulating chemicals. It is likely that a concentration of 100 ppt dioxin in blood, maintained for 2 years, is more toxic than the same concentration experienced for 1 week. The product of concentration and time is then a simple but suitable measure of exposure, more closely related to the effect than concentration. The AUC goes further by taking into account the fact that concentrations may change with time.

Bowman et al. (*3*) report that in a group of four of the rhesus monkeys used in Rier et al.'s study, the measured TCDD half-life ranged from 180 days to 788 days. After 4 years of exposure to 25 ppt TCDD in the diet, the whole-weight adipose tissue concentrations were in the range of 245–812 ppt. We assume that one-compartment kinetics apply for TCDD in monkeys and humans. Such an assumption is reasonable because TCDD is essentially stored in fat. Over time, the slow release from the fat compartment becomes the limiting factor of elimination from the body, and TCDD blood concentration at each time is proportional to the fat concentration. Standard results on multiple-dosing kinetics (*4*) give the AUC for adipose tissue concentration for these monkeys over a 14-year follow-up period (Table 1). These AUCs range from about 350,000 ppt × day to 1,400,000 ppt × day. The kinetic analysis also indicates that, after 4 years of exposure, concentration levels reached 72–99% of their steady-state values, depending on the animal.

Table 1. Toxicokinetic parameters and estimated area under the adipose tissue concentration curve (over 14 years) for rhesus monkeys exposed daily for 4 years to 25 ppt TCDD in diet

Monkey ID[a]	TCDD half-life[a] (days)	Adipose tissue conc.[a,b] (ppt)	Estimated AUC[c] (ppt × day)
PP91	180	245	358,000
PP100	788	665	1,312,000
PP104	540	812	1,395,000
PP110	491	735	1,227,000

[a]Data from Bowman et al. (*3*).
[b]Whole-weight adipose tissue concentration at the end of exposure.
[c]Area under curve (AUC) for a 14-year period (4-year exposure to 25 ppt and 10-year follow-up), assuming one-compartment kinetics.

Mocarelli et al. (*5*) provide, for 19 Seveso subjects (males and females), the concentration of TCDD in blood (lipid adjusted) at time of last known exposure (Table 2). Whole-weight adipose tissue concentration can be derived from blood concentration using the data of Patterson et al. (*6*) in occupationally exposed individuals. Whole-weight adipose tissue concentrations are obtained by dividing lipid-adjusted concentrations by a factor of 1.5; lipid-adjusted concentrations in adipose and serum are practically the same (*6*). For one woman (subject Seveso W), whole-weight adipose tissue concentration was directly measured (*6*) and does not need to be estimated. Given an estimated half-life for TCDD of 7 years in humans, taken to be independent of sex and age (*5,7*), it is easy to compute the AUC for whole-weight adipose tissue concentration for 1976–1993 (Table 2). The blood AUCs are expected to be proportional to those for adipose tissue and in the same proportion for both monkeys and humans. The portion of AUC from first to last contact time at Seveso was neglected because it is small compared to the rest of the area (the exposure period was only 1 or 2 months). These AUCs range from approximately 1,660,000 ppt × day to 112,000,000 ppt/day (on average 24,000,000 ppt × day). The AUCs exceed in all cases the values for monkeys exposed to 25 ppt and should also exceed those for the monkeys exposed to 5 ppt. For any subject, the AUC for 1976–1993 represents 85% of the AUC for 1976–2011, the latter being a measure of the total exposure potentially incurred by the Seveso subjects (assuming that on average they had half a lifetime, i.e., 35 years, left to live at the time of exposure). Therefore, the subjects have already received most of the total integrated exposure expected.

According to this analysis, it is likely that the total exposure to TCDD for some of the 1976 Seveso residents is much greater than that of the monkeys exhibiting endometriosis. Because the monkeys

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Table 2. Lipid-adjusted blood concentrations, estimated whole-weight adipose tissue concentrations, and estimated areas under the concentration curve for Seveso residents

Human ID[a]	Lipid-adjusted blood concentration[a] (ppt)	Whole-weight adipose tissue concentration[b] (ppt)	Estimated AUC[c] (ppt × day)
Seveso 01	56,000	37,333	112,052,000
Seveso 02	27,800	18,533	55,626,000
Seveso 03	26,400	17,600	52,825,000
Seveso 04	26,000	17,333	52,024,000
Seveso 05	15,900	10,600	31,815,000
Seveso 06	12,100	8,067	24,211,000
Seveso 07	17,300	11,533	34,616,000
Seveso 08	7,420	4,947	14,847,000
Seveso 09	1,690	1,127	3,382,000
Seveso 10	828	552	1,657,000
Seveso 11	10,400	6,933	20,810,000
Seveso 12	9,140	6,093	18,289,000
Seveso 13	6,320	4,213	12,646,000
Seveso 14	5,560	3,707	11,125,000
Seveso 15	4,540	3,027	9,084,000
Seveso 16	3,730	2,487	7,463,000
Seveso 17	3,050	2,033	6,103,000
Seveso 18	2,650	1,767	5,302,000
Seveso 19	1,770	1,180	3,542,000
Seveso W	NA[d]	1,840	5,523,000

[a]Concentration in the lipid fraction of the adipose tissue; data from Mocarelli et al. (*5*) and Patterson et al. (*6*).
[b]Obtained by dividing lipid-adjusted blood concentrations by a factor of 1.5 (see text).
[c]Area under curve (AUC) for whole-weight adipose tissue concentration was estimated assuming one-compartment kinetics and a half-life of 7 years for TCDD in humans.
[d]Not available; whole-weight adipose tissue concentration was directly measured for this subject (*6*).

exposed to 5 ppt in diet also had an increased risk of endometriosis, populations exposed to lower levels than those in Seveso may also be at increased risk if humans are at least as sensitive to the exposure as monkeys. To date, no epidemiologic study has investigated the gynecologic effects of TCDD; given its exposure, the

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